

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE 2004	3. REPORT TYPE AND DATES COVERED Journal Article-Clinical Science	
4. TITLE AND SUBTITLE Intermittent Altitude Exposures Reduce Acute Mountain Sickness at 4300 M			5. FUNDING NUMBERS	
6. AUTHOR(S) B.A. Beidleman, S.R. Muza, C.S. Fulco, A. Cymerman, D. Ditzler, D. Stulz, J.E. Staab, G.S. Skrinar, S.F. Lewis, M.N. Sawka				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Thermal & Mountain Medicine Division U.S. Army Research Institute of Environmental Medicine Kansas Street Natick, MA 01760-5007			8. PERFORMING ORGANIZATION REPORT NUMBER M02-56	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) Same as #7 above			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Distribution is unlimited.			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) Acute mountain sickness (AMS) commonly occurs at altitudes exceeding 2000-2500 m and usually resolves after acclimatization induced by a few days of chronic residence at the same altitude. Increased ventilation and diuresis may contribute to the reduction in AMS with altitude acclimatization. The aim of the present study was to examine the effects of intermittent altitude exposures (IAE), in combination with rest and exercise training, on the incidence and severity of AMS, resting ventilation and 24-h urine volume at 4300 m. Six lowlanders (age, 23 ± 2 years; body weight, 77 ± 6 kg; values are means ± S.E.M.) completed an Environmental Symptoms Questionnaire (ESQ) and Lake Louise AMS Scoring System (LLS), a resting end-tidal partial pressure of CO <sub>2</sub> (PETCO <sub>2</sub> ) test and a 24-h urine volume collection at sea level (SL) and during a 30 h exposure to 4300 m altitude-equivalent (barometric pressure = 446 mmHg) once before (PreIAE) and once after (PostIAE) a 3-week period of IAE (4 h/day-1, 5 days/week-1, 4300 m). The previously validated factor score, AMS cerebral score, was calculated from the ESQ and the self-report score was calculated from the LLS at 24 h of altitude exposure to assess the incidence and severity of AMS.				
14. SUBJECT TERMS acute mountain sickness, arterial oxygen saturation, hypobaric hypoxia, intermittent hypoxia, urine volume, ventilation			15. NUMBER OF PAGES 8	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unlimited	18. SECURITY CLASSIFICATION OF THIS PAGE Unlimited	19. SECURITY CLASSIFICATION OF ABSTRACT Unlimited	20. LIMITATION OF ABSTRACT Unlimited	

# Intermittent altitude exposures reduce acute mountain sickness at 4300 m

Beth A. BEIDLEMAN\*, Stephen R. MUZA†, Charles S. FULCO†, Allen CYMERMAN†, Dan DITZLER\*, Dean STULZ†, Janet E. STAAB†, Gary S. SKRINAR‡, Steven F. LEWIS‡ and Michael N. SAWKA†

\*Biophysics and Biomedical Modeling Division, United States Army Research Institute of Environmental Medicine, Natick, MA 01760, U.S.A., †Thermal and Mountain Medicine Division, United States Army Research Institute of Environmental Medicine, Natick, MA 01760, U.S.A., and ‡Department of Health Sciences, Sargent College of Health and Rehabilitation Sciences, Boston University, Boston, MA 02215, U.S.A.

## ABSTRACT

Acute mountain sickness (AMS) commonly occurs at altitudes exceeding 2000–2500 m and usually resolves after acclimatization induced by a few days of chronic residence at the same altitude. Increased ventilation and diuresis may contribute to the reduction in AMS with altitude acclimatization. The aim of the present study was to examine the effects of intermittent altitude exposures (IAE), in combination with rest and exercise training, on the incidence and severity of AMS, resting ventilation and 24-h urine volume at 4300 m. Six lowlanders (age,  $23 \pm 2$  years; body weight,  $77 \pm 6$  kg; values are means  $\pm$  S.E.M.) completed an Environmental Symptoms Questionnaire (ESQ) and Lake Louise AMS Scoring System (LLS), a resting end-tidal partial pressure of  $\text{CO}_2$  ( $P_{\text{ETCO}_2}$ ) test and a 24-h urine volume collection at sea level (SL) and during a 30 h exposure to 4300 m altitude-equivalent (barometric pressure = 446 mmHg) once before (PreIAE) and once after (PostIAE) a 3-week period of IAE ( $4 \text{ h} \cdot \text{day}^{-1}$ , 5 days  $\cdot \text{week}^{-1}$ , 4300 m). The previously validated factor score, AMS cerebral score, was calculated from the ESQ and the self-report score was calculated from the LLS at 24 h of altitude exposure to assess the incidence and severity of AMS. During each IAE, three subjects cycled for  $45\text{--}60 \text{ min} \cdot \text{day}^{-1}$  at 60–70 % of maximal  $\text{O}_2$  uptake ( $\dot{V}\text{O}_{2\text{max}}$ ) and three subjects rested. Cycle training during each IAE did not affect any of the measured variables, so data from all six subjects were combined. The results showed that the incidence of AMS (%), determined from both the ESQ and LLS, increased ( $P < 0.05$ ) from SL ( $0 \pm 0$ ) to PreIAE ( $50 \pm 22$ ) at 24 h of altitude exposure and decreased ( $P < 0.05$ ) from PreIAE to PostIAE ( $0 \pm 0$ ). The severity of AMS (i.e. AMS cerebral symptom and LLS self-report scores) increased ( $P < 0.05$ ) from SL ( $0.02 \pm 0.02$  and  $0.17 \pm 0.17$  respectively) to PreIAE ( $0.49 \pm 0.18$  and  $4.17 \pm 0.94$  respectively) at 24 h of altitude exposure, and decreased ( $P < 0.05$ ) from PreIAE to PostIAE ( $0.03 \pm 0.02$  and  $0.83 \pm 0.31$  respectively). Resting  $P_{\text{ETCO}_2}$  (mmHg) decreased (i.e. increase in ventilation;  $P < 0.05$ ) from SL ( $38 \pm 1$ ) to PreIAE ( $32 \pm 1$ ) at 24 h of altitude exposure and decreased further ( $P < 0.05$ ) from PreIAE to PostIAE ( $28 \pm 1$ ). In addition, 24-h urine volumes were similar at SL, PreIAE and PostIAE. In conclusion, our findings suggest that 3 weeks of IAE provide an effective alternative to chronic altitude residence for increasing resting ventilation and reducing the incidence and severity of AMS.

**Key words:** acute mountain sickness, arterial oxygen saturation, hypobaric hypoxia, intermittent hypoxia, urine volume, ventilation. **Abbreviations:** AMS, acute mountain sickness; AMS-C; AMS cerebral symptom; AMS-R; AMS respiration symptom; DBP, diastolic blood pressure; ESQ, Environmental Symptoms Questionnaire; HR, heart rate; IAE, intermittent altitude exposures; LLS, Lake Louise AMS Scoring System;  $P_{\text{B}}$ , barometric pressure;  $P_{\text{ETCO}_2}$ , end-tidal partial pressure of  $\text{CO}_2$ ;  $\text{SaO}_2$ , arterial  $\text{O}_2$  saturation; SBP, systolic blood pressure; SL, sea level;  $\dot{V}\text{O}_{2\text{max}}$ , maximal  $\text{O}_2$  uptake.

**Correspondence:** Dr Beth A. Beidleman (e-mail [beth.beidleman@na.amedd.army.mil](mailto:beth.beidleman@na.amedd.army.mil)).

## INTRODUCTION

Acute mountain sickness (AMS) is a syndrome induced by hypoxia in unacclimatized individuals who ascend rapidly to altitudes exceeding 2500 m and remain there for more than several hours [1–4]. Characteristic symptoms include headache, nausea, vomiting, loss of appetite, fatigue, dizziness and sleep disturbances [2,4–7]. The onset of AMS usually occurs 4–12 h after ascent, and symptoms become most prominent after the first night spent at high altitude. Resolution of AMS usually occurs following altitude acclimatization induced by 1–2 days of high-altitude residence if no further ascent is attempted [3,8]. Increased ventilation and diuresis, which can occur over the same few days of high-altitude residence, may contribute to the resolution of AMS with altitude acclimatization [3,8–10].

Although a few days of high-altitude residence significantly reduces the incidence and severity of AMS symptoms, athletes or military units rapidly deployed to high altitude may be completely incapacitated by AMS during the first few days at a new altitude. Thus current guidance suggests the use of slow or staged ascent profiles to induce altitude acclimatization and reduce the debilitating effects associated with the initial occurrence of AMS [1,11,12]. However, for many occupations and recreational activities, participants may not have sufficient time and logistical support to utilize these staged ascent profiles. Alternatively, acetazolamide provides an effective pharmacological prophylaxis for AMS upon rapid ascent to high altitude [2,13–15], but may have side effects, including gastric distress, nausea, constipation, fatigue and paresthesia. A promising alternative approach to induce altitude acclimatization and reduce the incidence and severity of AMS is the use of intermittent altitude exposures (IAE). Even though descriptive improvements in altitude illness have been reported following IAE [16,17], the incidence and severity of AMS has not been quantitatively measured before and after IAE in a group of lowlanders. In addition, the relationship between changes in the severity of AMS and changes in arterial  $O_2$  saturation ( $SAO_2$ ) and 24-h urine volumes following IAE have not been reported.

Even though performing exercise while ascending to altitude has been shown to increase symptoms of AMS [18], possibly due to increased hypoxaemia and sodium retention [19], the use of moderate exercise in combination with residence at altitude may enhance the magnitude of acclimatization, due to the exacerbation of arterial hypoxaemia during exercise at 4300 m. If exercising at 60–70 % of maximal  $O_2$  uptake ( $\dot{V}O_{2\max}$ ) at 4300 m induces a 5–10 % arterial desaturation [20,21], this amount of desaturation is equivalent to sitting at an altitude of approx. 5000–5500 m [22]. Thus the addition of exercise at a given altitude is another way of providing a greater hypoxic stress (i.e. 'higher altitude exposure') to the body

without increasing the exposure altitude and may induce a greater degree of acclimatization.

The aim of the present study, therefore, was to examine the effects of 3 weeks of IAE ( $4\text{ h}\cdot\text{day}^{-1}$ , 5 days  $\cdot\text{week}^{-1}$ , 4300 m) on the incidence and severity of AMS symptoms, resting ventilation and 24-h urine volume. We hypothesized that 3 weeks of IAE would reduce the incidence and severity of AMS symptoms at 4300 m and that the reduction in AMS severity would be associated with an increase in resting ventilation (i.e., increase in  $SAO_2$ ) and 24-h urine volume. We also hypothesized that cycle training during the 3 weeks of IAE would reduce further the incidence and severity of AMS symptoms related to the exacerbation of arterial hypoxaemia during cycle training sessions.

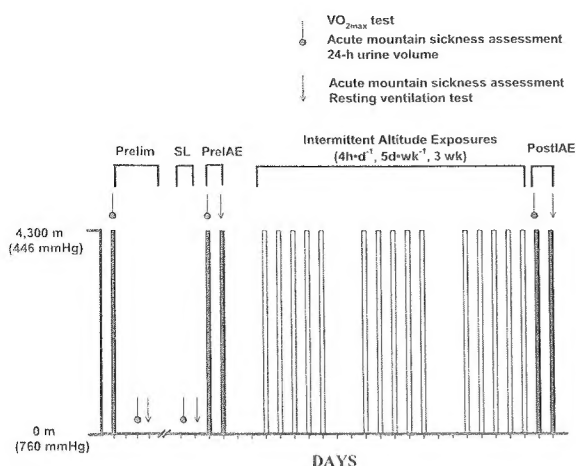
## METHODS

### Volunteer test subjects

Eight non-smoking volunteers (six men and two women) enrolled in the study. Two volunteers dropped out during the study and, therefore, six non-smoking volunteers (five men and one woman) with a mean ( $\pm$  S.E.M.) age and body weight of  $23 \pm 2$  years and  $77 \pm 6$  kg respectively, participated. Each was a life-long low-altitude resident and had no exposure to altitudes greater than 1000 m for at least 6 months immediately preceding the study. All volunteers received medical examinations, and none had any condition warranting exclusion from the study. All had normal haemoglobin and serum ferritin levels. The woman had a normal menstrual cycle length ( $28 \pm 1$  days) over the 2-month testing period, had not taken oral contraceptives or hormone therapy for the previous 6 months and had never been pregnant. Testing was not controlled for menstrual cycle phase, because AMS cerebral (AMS-C), AMS respiration (AMS-R) and Lake Louise AMS Scoring System (LLS) self-report symptom scores do not differ between the follicular and luteal phases of the menstrual cycle at 4300 m [23]. All volunteers performed regular sea-level (SL) aerobic training ( $1\text{--}2\text{ h}\cdot\text{week}^{-1}$ ) before and during the study to maintain pre-study level of SL physical fitness. All were of average physical fitness. Each gave written and verbal acknowledgment of their informed consent and was made aware of their right to withdraw without prejudice at any time. The research was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Investigators have adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 45 Code of Federal Regulations Part 46.

### Study design

The study used an unblinded two-factor (test condition and group) experimental design. The test conditions



**Figure 1** Study design

Each test volunteer's incidence and severity of AMS, resting ventilation and 24-h urine volume were measured during preliminary measurements (Prelim), at SL, and during a 30 h exposure to 4300 m altitude-equivalent ( $P_B = 446$  mmHg) once before (PreIAE) and once after (PostIAE) a 3-week period of IAE ( $4 \text{ h} \cdot \text{day}^{-1}$ ;  $5 \text{ days} \cdot \text{week}^{-1}$ , 4300 m). Modified from [24] with permission. © (2003) American Physiological Society.

were defined as SL, before IAE (PreIAE) and after IAE (PostIAE). The groups were defined as rest and cycle training during IAE. Each test volunteer's incidence and severity of AMS, resting ventilation and 24-h urine volume were measured at SL and during a 30 h exposure to 4300 m altitude-equivalent [barometric pressure ( $P_B$ ) = 446 mmHg] once before (PreIAE) and once after (PostIAE) a 3-week period of IAE ( $4 \text{ h} \cdot \text{day}^{-1}$ ;  $5 \text{ days} \cdot \text{week}^{-1}$ , 4300 m) (Figure 1). Each volunteer's  $\dot{V}O_{2\text{max}}$  and maximal heart rate (HR) were also determined within approx. 4–6 h of exposure to SL, PreIAE and PostIAE and these results have been reported previously [24]. To minimize the impact of potential learning effects, all volunteers completed a preliminary Environmental Symptoms Questionnaire (ESQ) and LLS at 4300 m and SL and a resting end-tidal partial pressure of  $\text{CO}_2$  ( $P_{\text{ETCO}_2}$ ) test and 24-h urine volume collection at SL prior to definitive data collection.

### IAE

In the morning before each IAE, volunteers were weighed (wearing t-shirts, shorts and socks). If body weight had changed by more than  $\pm 1$  kg from baseline during the morning weigh-in, volunteers were encouraged to eat more or less depending on the direction of body weight change, in order to maintain constant body weight throughout the study. During each IAE, the three volunteers randomly assigned to the resting group sat in their bunks, watched television, listened to music, read books and wrote letters for the 4 h altitude exposure. In contrast, the three volunteers randomly assigned to the exercise training group exercised for approx. 45–

60 min, starting within 15 min of arriving at altitude, and rested for the remainder of the 4 h altitude exposure. The exercise performed during each IAE consisted of continuous constant work rate and interval training on a cycle ergometer (Model 818E; Monark, Varberg, Sweden) at an intensity corresponding to approx. 70–85 % of pre-training altitude maximal HR. As exercise training progressed, cycle work rates were adjusted, if necessary, to ensure achievement of appropriate training HR during each training session. Systolic blood pressure (SBP) and diastolic blood pressure (DBP), using a sphygmomanometer (Baumanometer; W. A. Baum, Copiague, NY, U.S.A.),  $\text{SaO}_2$ , using a finger pulse oximeter (Model N-200; Nellcor, Pleasanton, CA, U.S.A.), and HR, using a wireless HR watch (Model 8799, Computer Instruments, Hempstead, NY, U.S.A.), were periodically measured on both groups of volunteers. Mean arterial pressure was calculated as  $0.333 \times (\text{SBP} - \text{DBP}) + \text{DBP}$ .

At the end of each training session, all volunteers remained resting in the hypobaric chamber, so that their total exposure time to hypobaric hypoxia, including a 15 min decompression and 15 min recompression, was  $4 \text{ h} \cdot \text{day}^{-1}$ . Volunteers were encouraged to drink water to replace any fluid loss during exercise and/or altitude exposure. All volunteers were required to maintain (i.e. not increase or decrease) their  $1\text{--}2 \text{ h} \cdot \text{week}^{-1}$  aerobic training at SL to maintain their pre-study level of physical fitness. Physical activity monitor logs were kept throughout the 5 week study.

### Environmental conditions

All testing and training were performed in a hypobaric chamber that was maintained at a temperature and relative humidity of  $21 \pm 2^\circ\text{C}$  and  $45 \pm 5\%$  respectively. The SL testing was performed at ambient barometric pressure (approx. 760 mm Hg), and all altitude exposures were conducted at an altitude-equivalent of 4300 m ( $P_B = 446$  mmHg).

### Diet

The quantity of food consumed was not limited; however, to limit the potential effects that diet may have on the incidence and severity of AMS symptoms [25], volunteers were given meals of identical nutrient and caloric content during each 30-h test condition at SL, PreIAE and PostIAE. Food intake was recorded and analysed for energy content and percentage contribution of macronutrients (Nutritionist III v.6.0; N-Squared Computing, Silverton, OR, U.S.A.). Urine volumes over 24 h were recorded during the first 24 h of testing at SL, PreIAE and PostIAE. At no time during the entire study were volunteers allowed to consume caffeine.

### Resting ventilation

Resting ventilation measurements were performed in a fasted condition after approx. 20–22 h exposure to each

test condition. Volunteers sat in a semi-recumbent position and breathed through a low-resistance respiratory valve and breathing circuit connected to a computer-controlled, breath-by-breath open circuit metabolic measurement system (Vmax229; SensorMedics, Yorba Linda, CA, U.S.A.). Resting values were obtained for minute ventilation and  $PETCO_2$ . Resting  $SAO_2$  was measured by pulse oximetry (Model N-200; Nellcor, Pleasanton, CA, U.S.A.) and resting HR was measured by three-lead ECG (Model N-200; Nellcor). The duration of the resting ventilation tests was approx. 20 min. Mean resting ventilation data were calculated from the last 8–10 min of the session.

### Altitude illness assessment

Incidence and severity of AMS symptoms were determined from information gathered using the ESQ and LLS. The ESQ is a self-reported, 68-question inventory designed to quantify symptoms induced by altitude and other stressful environments [26]. Symptom severity is self-rated on a scale of 0–5, with a score of 0 indicating the absence of symptoms and 5 representing the symptom present at maximum intensity. A weighted average of cerebral symptoms (headache, light-headed and dizzy; designated AMS-C) and respiratory symptoms (i.e. short-of-breath and hurts-to-breathe; designated AMS-R) was calculated for each subject for each AMS assessment. AMS was judged to be present if an individual's AMS-C score was  $\geq 0.7$  or AMS-R score was  $\geq 0.6$ . The effectiveness of AMS-C scores in identifying individuals with AMS has been reported and validated previously [26].

The LLS consists of a five-question, self-reported assessment of five AMS symptoms using a scale of 0–3 and an investigator-conducted assessment of three clinical signs of AMS [27]. The LLS self-report and LLS self-report plus clinical assessment scores were calculated for each test volunteer and the presence of AMS was defined as headache (i.e. score of  $\geq 1$  on the headache question) plus one additional symptom of AMS for a total score of  $\geq 3$  on either the self-report questionnaire alone or in combination with the clinical assessment after exposure to altitude for more than 2 h [27]. The LLS self-report scoring system has been demonstrated to reliably detect the presence of AMS and correlate with ESQ scores [28,29].

The incidence of AMS for both the ESQ and LLS scoring instruments was defined as the number of test volunteers who achieved or exceeded the criterion score value on a measure of AMS for the first time during the 30 h exposure divided by the total number of test volunteers. Symptoms of AMS were assessed four times at SL (14:00, 20:00, 08:00 and 14:00 hours) using ESQ and LLS. Both the ESQ and LLS questionnaires were administered four times (14:00, 20:00, 08:00 and 14:00 hours) during each 30 h altitude condition. Given

**Table 1** Combined group body weight, height, energy intake and percentage contribution of carbohydrate, fat and protein to the diet ( $n = 6$ )

Values are means  $\pm$  S.E.M. 1 kcal  $\equiv$  4.184 kJ.

	SL	PreIAE	PostIAE
Body weight (kg)	77 $\pm$ 6	77 $\pm$ 6	77 $\pm$ 6
Height (cm)	177 $\pm$ 3		
Energy intake (kcal)	2815 $\pm$ 194	1853 $\pm$ 257	2135 $\pm$ 319
Urine volume on day 1 (ml $\cdot$ 24 h $^{-1}$ )	1587 $\pm$ 336	2408 $\pm$ 614	2133 $\pm$ 674
Contribution to diet (%)			
Carbohydrate	58 $\pm$ 3	56 $\pm$ 5	55 $\pm$ 2
Fat	28 $\pm$ 3	31 $\pm$ 4	34 $\pm$ 2
Protein	14 $\pm$ 3	13 $\pm$ 1	11 $\pm$ 2

that volunteers started each 30 h test condition at approx. 08:00 hours, these time points corresponded to 6, 12, 24 and 30 h post-exposure.

### Statistical analyses

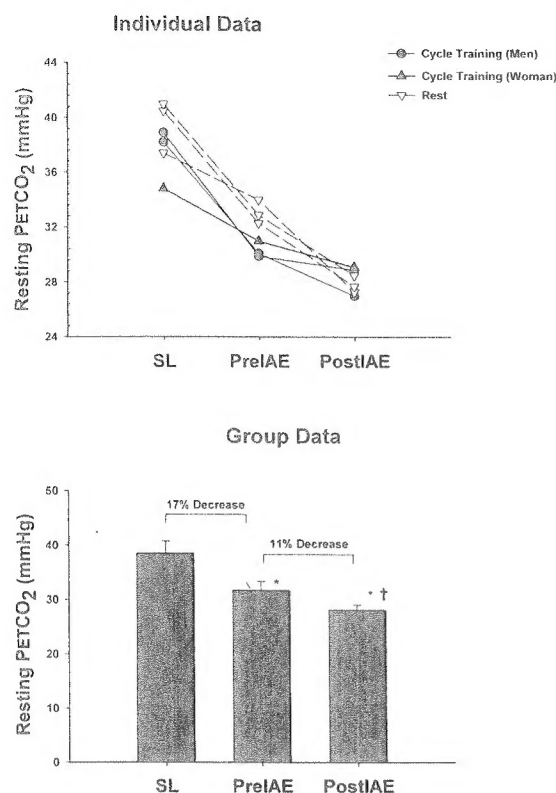
A two-way repeated measures ANOVA was used to analyse differences between the independent group factor (rest and exercise training) and the repeated measures test condition factor (SL, PreIAE, and PostIAE) for the incidence of AMS, resting  $PETCO_2$ ,  $SAO_2$  and 24-h urine volume measurements. Three-way ANOVAs, with repeated measures on the additional factor of time, were used for AMS-C, AMS-R and LLS scores. Significant main effects and interactions were analysed using Tukey's least significant difference test. Pearson product-moment correlation coefficients were calculated for the relationships between the change in the severity of AMS and changes in  $SAO_2$  and 24-h urine volume from SL to PreIAE and PreIAE to PostIAE. Statistical significance was set at  $P < 0.05$ . All data are presented as means  $\pm$  S.E.M.

## RESULTS

Even though arterial  $O_2$  desaturation was 5–10 % greater during cycle training compared with rest during each IAE, cycle training did not reduce further the incidence or severity of AMS or affect any of the other measured variables. Thus, for statistical analyses, data from all six subjects were combined. Individual responses are provided for  $PETCO_2$ .

### Volunteer test subjects

Mean body weights, heights, 24-h urine volumes, energy intakes and percentage contributions of carbohydrate, fat and protein to the diet were similar among testing conditions (Table 1). Mean body weight did not change from baseline during the 5-week course of the study.



**Figure 2** Effect of IAE on  $PETCO_2$

$PETCO_2$  (mmHg) was measured in six volunteers at SL and during  $\leq 30$  h exposures to 4300 m altitude-equivalent ( $P_B = 446$  mmHg) before (PreIAE) and immediately after (PostIAE) a 3 week period of IAE ( $4 \text{ h} \cdot \text{day}^{-1}$ ;  $5 \text{ days} \cdot \text{week}^{-1}$ , 4300 m). \* $P < 0.05$  compared with SL, † $P < 0.05$  compared with PreIAE.

### Resting ventilation

Individual and group  $PETCO_2$  data (mmHg) are shown in Figure 2. All individuals exhibited a decrease in  $PETCO_2$  (i.e. increase in ventilation) from SL to PreIAE. All individuals exhibited a further decrease in  $PETCO_2$  from PreIAE to PostIAE. The mean  $PETCO_2$  decreased by  $17 \pm 6\%$  ( $P < 0.05$ ) from SL ( $38.5 \pm 0.9$  mmHg) to PreIAE ( $31.7 \pm 0.7$  mmHg) and decreased further by  $11 \pm 6\%$  from PreIAE to PostIAE ( $28.0 \pm 0.3$  mmHg). Resting  $SAO_2$  decreased ( $P < 0.05$ ) from SL ( $99 \pm 1\%$ ) to PreIAE ( $80 \pm 2\%$ ) and increased ( $P < 0.05$ ) from PreIAE to PostIAE ( $85 \pm 1\%$ ). Resting HR increased ( $P < 0.05$ ) from SL ( $64 \pm 7$  beats/min) to PreIAE ( $86 \pm 11$  beats/min) and decreased ( $P < 0.06$ ) from PreIAE to PostIAE ( $75 \pm 8$  beats/min).

### AMS

AMS-C, AMS-R, LLS self-report and LLS self-report plus clinical symptom scores are shown in Figure 3. The AMS-C score, measured at 12, 24 and 30 h post-altitude exposure, increased ( $P < 0.05$ ) from SL to PreIAE and decreased ( $P < 0.05$ ) from PreIAE to PostIAE. The AMS-R score was similar at SL, PreIAE and PostIAE at all time

points. The LLS self-report and LLS self-report plus clinical scores, measured at 12, 24 and 30 h post-altitude exposure, increased ( $P < 0.05$ ) from SL to PreIAE and decreased ( $P < 0.05$ ) from PreIAE to PostIAE. The AMS-C and LLS self-report scores were correlated at PreIAE at 6 h ( $r = 0.89$ ,  $P = 0.02$ ), 12 h ( $r = 0.95$ ,  $P = 0.003$ ), 24 h ( $r = 0.92$ ,  $P = 0.009$ ) and 30 h ( $r = 0.93$ ,  $P = 0.008$ ). The increase in AMS-C from SL to PreIAE, measured at 24 h post-exposure, was significantly correlated with the decrease in resting  $SAO_2$ , measured at 24 h post exposure, from SL to PreIAE ( $r = -0.82$ ,  $P = 0.05$ ). The decrease in AMS-C from PreIAE to PostIAE, measured at 24 h post-exposure, was significantly correlated with the increase in resting  $SAO_2$ , measured at 24 h post-exposure, from PreIAE to PostIAE ( $r = -0.82$ ,  $P = 0.04$ ). The change in 24-h urine volume from one test condition to the next was not related to the change in the AMS-C or LLS self-report scores.

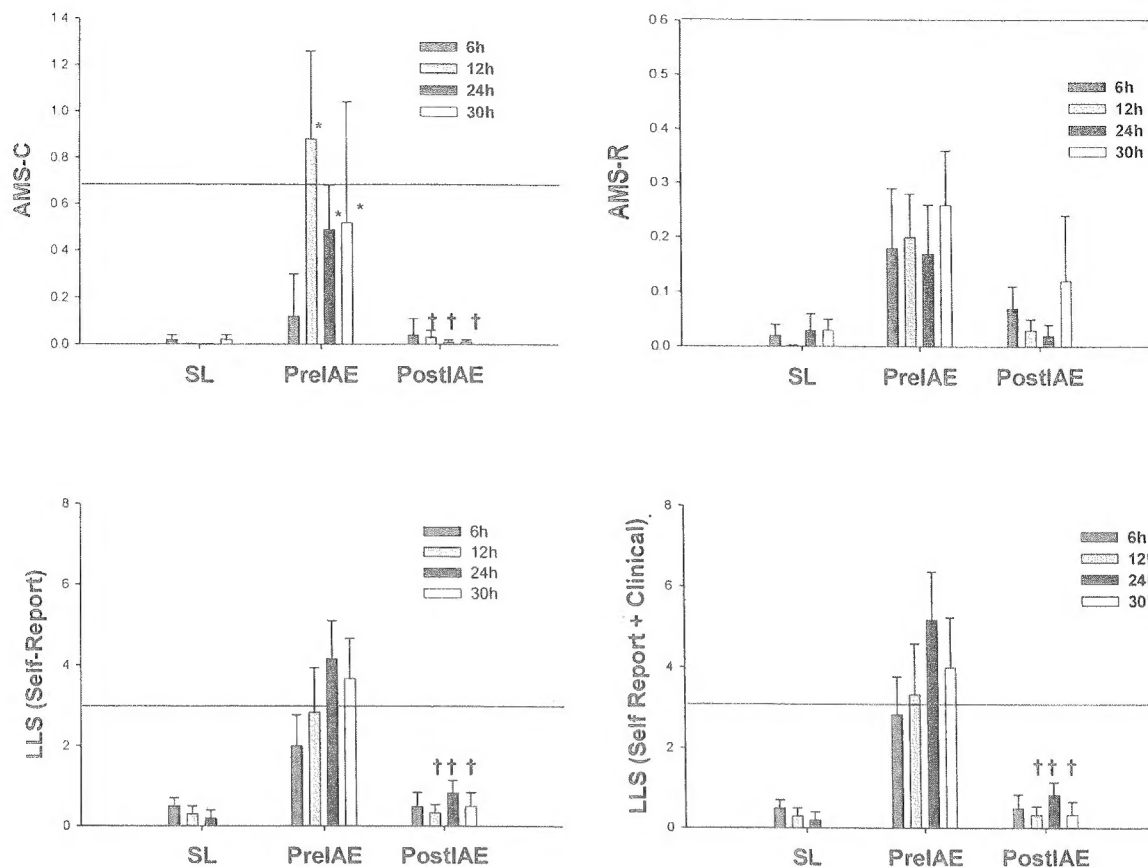
The incidence of AMS, determined from both the ESQ and LLS scoring instruments, was identical at all time points. The incidence of AMS increased ( $P < 0.05$ ) from SL ( $0 \pm 0$  and  $0 \pm 0\%$ ) to PreIAE ( $50 \pm 22$  and  $50 \pm 22\%$ ) at 24 and 30 h of altitude exposure respectively, and decreased ( $P < 0.05$ ) at PostIAE ( $0 \pm 0$  and  $0 \pm 0\%$  respectively) compared with PreIAE. Resting HR and mean arterial pressure collected every other day during intermittent altitude exposures did not change from day 1 to day 15. Resting  $SAO_2$  increased ( $P < 0.05$ ) from day 1 to day 15 of IAE (Figure 4).

### DISCUSSION

The present study tested the hypothesis that 3 weeks of IAE, in combination with rest or cycle training, would reduce the incidence and severity of AMS at 4300 m and that the reduction in AMS severity would be associated with an increase in resting ventilation and 24-h urine volume. The present study makes the following new conclusions following 3 weeks of IAE: (i) the incidence and severity of AMS during a 30 h exposure to 4300 m were reduced, and (ii) the reduction in the severity of AMS was related to the increase in resting  $SAO_2$ , but not 24-h urine volume. The reductions in the incidence and severity of AMS following 3 weeks of IAE were quantifiably comparable with those reported previously following chronic altitude residence [30–32]. IAE may therefore be used as an alternative to chronic altitude residence to reduce the incidence and severity of AMS upon exposure to 4300 m.

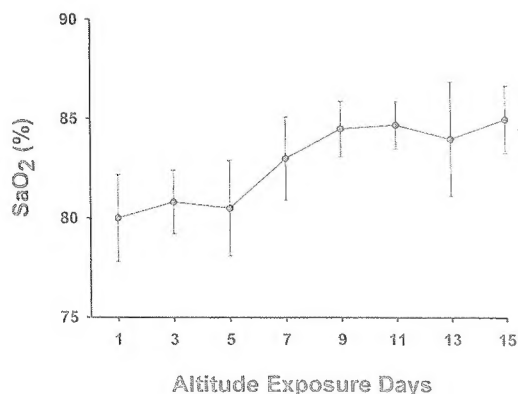
Two commonly proposed mechanisms for the development of AMS upon exposure to altitude are the absence of normal altitude diuresis, evidenced by a lack of increased urine output [3,10,33], and relative hypoventilation [9,10,34]. The most likely explanation for the reduction in the incidence and severity of AMS





**Figure 3** AMS-C, AMS-R, LLS self-report and LLS self-report plus clinical assessment scores during IAE

AMS-C, AMS-R, LLS self-report [LLS (Self-report)] and LLS self-report and clinical assessment score [LLS (Self-report + Clinical)] were measured in six volunteers at 6, 12, 24 and 30 h of exposure to SL, during  $\leq 30$  h exposures to 4300 m altitude-equivalent ( $P_B = 446$  mmHg) before (PreIAE) and immediately after (PostIAE) a 3 week period of IAE ( $4 \text{ h} \cdot \text{day}^{-1}$ ; 5 days  $\cdot \text{week}^{-1}$ , 4300 m). \*  $P < 0.05$  compared with SL. †  $P < 0.05$  compared with PreIAE.



**Figure 4** Resting  $\text{SaO}_2$  during IAE

Resting  $\text{SaO}_2$  measured every other day in six volunteers during 15 days of IAE. \*  $P < 0.05$  compared with day 1.

following 3 weeks of IAE in the present study was the increase in resting ventilation and corresponding increase in  $\text{SaO}_2$ , since 24-h urine volume was not changed. Since

resting  $\text{SaO}_2$  ( $80 \pm 2\%$ ) during the first 30 h exposure to 4300 m (i.e. PreIAE) was the same as the resting  $\text{SaO}_2$  ( $80 \pm 2\%$ ) at 4300 m on the first day of IAE, it is unlikely that resting ventilation increased due to the stimulus of the initial 30 h altitude exposure. Although an increase in hypoxic ventilatory sensitivity has been reported after as little as 8 h of exposure to poikilocapnic hypoxia [35], it has also been shown [36] that the increased hypoxic ventilatory sensitivity following 16 days of acclimatization to 4300 m decreases back to SL values following 5 days of altitude deacclimatization. Although not measured, the  $\sim 3$  days of altitude deacclimatization from PreIAE to the first day of IAE in our present study would most probably return hypoxic ventilatory sensitivity back to SL values following a relatively short 30 h altitude exposure. Thus the observed increase in resting ventilation at PostIAE was most probably due to the 15 days of IAE and not the initial 30 h altitude exposure.

The increase in resting ventilation and  $\text{SaO}_2$  following repeated IAE has been reported in most [21,37–40], but not all [41], previous studies. However, the present study

is the first in which the change in resting  $\text{SaO}_2$  has been correlated with the change in the severity of AMS following IAE. The strong correlations between the increase in AMS-C and decrease in resting  $\text{SaO}_2$  from SL to PreIAE, as well as the strong correlation between the decrease in AMS-C and increase in resting  $\text{SaO}_2$  from PreIAE to PostIAE, supports the hypothesis that resting  $\text{SaO}_2$  is closely linked with AMS severity.

This is the first study to report that IAE result in the complete elimination of AMS in lowlanders. Although several other studies have suggested that AMS is eliminated following IAE [16,17], none have quantitatively measured AMS. One study [42] did quantitatively measure AMS in lowlanders upon exposure to 4500 m following intermittent exposures to hypoxic gases ( $8 \text{ h} \cdot \text{day}^{-1}$ , 10 days, 3200–3500 m) and compared their responses with a group of non-acclimatized controls. That study [42] reported no differences in the severity of AMS between groups upon exposure to 4500 m, but was complicated by the fact that up to five breaks of varying duration were given from breathing the hypoxic gases during the course of the 8-h day. Furthermore, even though the inspired partial pressure of  $\text{O}_2$  ( $P_{\text{O}_2}$ ) was known, the actual degree of hypoxaemia (i.e.  $\text{SaO}_2$ ) was not measured in the volunteers breathing the hypoxic gas mixture. Thus these earlier results are tenuous at best.

The incidence and severity of AMS upon acute exposure to altitude in our present study was comparable with the mean results reported from other altitude studies conducted at 4300 m [30–32]. However, this is the first study to report that intermittent exposures to 4300 m were equally as effective as chronic altitude residence [30–32] in eliminating the incidence and severity of AMS. IAE therefore appear to be an effective alternative to chronic altitude residence for inducing altitude acclimatization and eliminating AMS.

During the 15 days of IAE, resting  $\text{SaO}_2$  was increased from the first day to the last day of exposure (Figure 4). The pattern of increase, however, did not appear linear, in that the majority of the increase in  $\text{SaO}_2$  occurred by day 9. Although we had hoped to determine whether we could shorten the number of altitude exposure days needed to acclimatize to 4300 m, the lack of a statistically significant change in  $\text{SaO}_2$ , a major determinant of altitude acclimatization, until the 15th day of altitude exposure suggests otherwise.

## Conclusions

The present study makes the following new conclusions following 3 weeks of IAE: (i) the incidence and severity of AMS during a 30 h exposure to 4300 m were reduced, and (ii) the reduction in the severity of AMS was related to the increase in resting  $\text{SaO}_2$ , but not 24-h urine volume.

The reductions in the incidence and severity of AMS following 3 weeks of IAE were comparable with those reported previously following chronic altitude residence. IAE may therefore be used as an alternative to chronic altitude residence to reduce the incidence and severity of AMS upon exposure to 4300 m.

## ACKNOWLEDGMENTS

We thank the test volunteers for their participation and co-operation in this study. We gratefully acknowledge the technical and logistical support provided by Sergeant Dave DeGroot, Sergeant James Moulton, Mr Vinnie Forte, Jr and Mr Scott Robinson. The efforts of all chamber crew operators and medical support staff are also gratefully acknowledged. The views, opinions and/or findings in this report are those of the authors, and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other official documentation. Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

## REFERENCES

- Johnson, T. S. and Rock, P. B. (1988) Acute mountain sickness. *N. Engl. J. Med.* **319**, 841–845
- Hackett, P. H. and Rennie, D. (1976) The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet* **ii**, 1149–1154
- Singh, I., Khanna, P. K., Srivastava, M. C., Lal, M., Roy, S. B. and Subramanyam, C. S. V. (1969) Acute mountain sickness. *N. Engl. J. Med.* **280**, 175–184
- Honigman, B., Thesis, M. K. and Koziol-McLain, J. (1993) Acute mountain sickness in a general tourist population at moderate altitude. *Ann. Intern. Med.* **118**, 587–592
- Bailey, D. M., Davies, B., Milledge, J. S. et al. (2000) Elevated plasma cholecystokinin at high altitude: metabolic implications for the anorexia of acute mountain sickness. *High Alt. Med. Biol.* **1**, 9–23
- Sanchez del Rio, M. and Moskowitz, M. A. (1999) High altitude headache: lessons from headaches at sea level. *Adv. Exp. Med. Biol.* **474**, 145–153
- Powles, A. P. and Sutton, J. R. (1983) Sleep at altitude. *Semin. Respir. Med.* **5**, 175–180
- Bärtsch, P., Shaw, S., Franciolli, M., Gnadinger, M. P. and Weidmann, P. (1988) Atrial natriuretic peptide in acute mountain sickness. *J. Appl. Physiol.* **65**, 1929–1937
- Moore, L. G., Harrison, G. L., McCullough, R. E. et al. (1986) Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. *J. Appl. Physiol.* **60**, 1407–1412
- Hackett, P. H., Rennie, D., Hofmeister, S. E., Grover, R. F., Grover, E. B. and Reeves, J. T. (1982) Fluid retention and relative hypoventilation in acute mountain sickness. *Respiration* **43**, 321–329
- Hansen, J. E., Harris, C. W. and Evans, W. O. (1967) Influence of elevation of origin, rate of ascent and a physical conditioning program on symptoms of acute mountain sickness. *Mil. Med.* **132**, 585–592
- Purkayastha, S. S., Ray, U. S., Arora, B. S. et al. (1995) Acclimatization at high altitude in gradual and acute induction. *J. Appl. Physiol.* **79**, 487–492



- 13 Larsen, E. B., Roach, R. C., Schoene, R. B. and Hornbein, T. F. (1982) Acute mountain sickness and acetazolamide. Clinical efficacy and effect on ventilation. *JAMA, J. Am. Med. Assoc.* **248**, 328–332
- 14 Forwand, S. A., Landowne, M., Follansbee, J. N. and Hansen, J. E. (1968) Effect of acetazolamide on acute mountain sickness. *N. Engl. J. Med.* **279**, 839–845
- 15 Greene, M. K., Kerr, A. M., McIntosh, I. B. and Prescott, R. J. (1981) Acetazolamide in prevention of acute mountain sickness: a double-blind controlled cross-over study. *Br. Med. J.* **283**, 811–813
- 16 Rodriguez, F. A., Casas, H., Casas, M. et al. (1999) Intermittent hypobaric hypoxia stimulates erythropoiesis and improves aerobic capacity. *Med. Sci. Sports Exercise* **31**, 264–268
- 17 Casas, M., Casas, H., Pages, T. et al. (2000) Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. *Aviat. Space Environ. Med.* **71**, 125–130
- 18 Roach, R. C., Maes, D., Sandoval, D. et al. (2000) Exercise exacerbates acute mountain sickness at simulated high altitude. *J. Appl. Physiol.* **88**, 581–585
- 19 Withey, W. R., Milledge, J. S., Williams, E. S. et al. (1983) Fluid and electrolyte homeostasis during prolonged exercise at altitude. *J. Appl. Physiol.* **55**, 409–412
- 20 Beidleman, B. A., Rock, P. B., Muza, S. R., Fulco, C. S., Forte, Jr, V. A. and Cymerman, A. (1999) Exercise  $V_E$  and physical performance are not affected by menstrual cycle phase at altitude. *J. Appl. Physiol.* **86**, 1519–1526
- 21 Katayama, K., Sato, Y., Ishida, K., Mori, S. and Miyamura, M. (1998) The effects of intermittent exposure to hypoxia during endurance exercise training on the ventilatory responses to hypoxia and hypercapnia in humans. *Eur. J. Appl. Physiol.* **78**, 189–194
- 22 Ward, M. P., Milledge, J. S. and West, J. B. (2000) The atmosphere. In *High Altitude Medicine and Physiology*, 3rd edn, pp. 22–32, Chapman & Hall Medical, London
- 23 Rock, P. B., Muza, S. R., Fulco, C. S. et al. (2001) Women at altitude: effect of menstrual-cycle phase on acute mountain sickness during deployment to high altitude terrain. USARIEM Technical Report, T01–T18, Natick, MA
- 24 Beidleman, B. A., Muza, S. R., Fulco, C. S. et al. (2003) Intermittent altitude exposures improve muscular performance at 4300 m. *J. Appl. Physiol.* **95**, 1824–1832
- 25 Consolazio, C. F., Matoush, L. O., Johnson, H. L., Krzywicki, H. J., Daws, T. A. and Isaac, G. J. (1969) Effects of high-carbohydrate diets on performance and clinical symptomatology after rapid ascent to high altitude. *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **28**, 937–943
- 26 Sampson, J. B., Kobrick, J. L. and Johnson, R. F. (1994) Measurement of subjective reactions to extreme environments: the Environmental Symptoms Questionnaire. *Mil. Psychol.* **6**, 215–233
- 27 Roach, R. C., Bartsch, P., Oelz, O., Hackett, P. H. and Lake Louise AMS Scoring Consensus Committee (1993) The Lake Louise acute mountain sickness scoring system. In *Hypoxia and Molecular Biology* (Sutton, J. R., Houston, C. S. and Coates, G., eds.), pp. 272–274, Queen City Press, Burlington
- 28 Maggiorini, M., Muller, A., Hofstetter, D., Bartsch, P. and Oelz, O. (1998) Assessment of acute mountain sickness by different score protocols in the Swiss Alps. *Aviat. Space Environ. Med.* **69**, 1186–1192
- 29 Savourey, G. A., Guinet, A., Besnard, Y., Garcia, N., Hanniquet, A. M. and Bittel, J. (1995) Evaluation of the Lake Louise acute mountain sickness scoring system in a hypobaric chamber. *Aviat. Space Environ. Med.* **66**, 963–967
- 30 Fulco, C. S., Rock, P. B., Reeves, J. T., Trad, L. A., Young, P. M. and Cymerman, A. (1989) Effects of propranolol on acute mountain sickness (AMS) and well-being at 4,300 meters of altitude. *Aviat. Space Environ. Med.* **60**, 679–683
- 31 Rock, P. B., Johnson, T. S., Cymerman, A., Burse, R. L., Falk, L. J. and Fulco, C. F. (1987) Effect of dexamethasone on symptoms of acute mountain sickness at Pikes Peak, Colorado (4,300 m). *Aviat. Space Environ. Med.* **58**, 668–672
- 32 Lyons, T. P., Muza, S. R., Rock, P. B. and Cymerman, A. (1995) The effect of altitude pre-acclimatization on acute mountain sickness during reexposure. *Aviat. Space Environ. Med.* **66**, 957–962
- 33 Westerterp, K. R., Robach, P., Wouters, L. and Richalet, J. P. (1996) Water balance and acute mountain sickness before and after arrival at high altitude of 4,350 m. *J. Appl. Physiol.* **80**, 1968–1972
- 34 Roach, R. C., Greene, E. R., Schoene, R. B. and Hackett, P. H. (1998) Arterial oxygen saturation for prediction of acute mountain sickness. *Aviat. Space Environ. Med.* **69**, 1182–1185
- 35 Howard, L. S. and Robbins, P. A. (1995) Alterations in respiratory control during 8 h of isocapnic and poikilocapnic hypoxia in humans. *J. Appl. Physiol.* **78**, 1092–1097
- 36 Muza, S. R., Fulco, C. S., Lyons, T. et al. (1995) Augmented chemosensitivity at altitude and after return to sea level: impact on subsequent return to altitude. *Acta Andina* **4**, 109–112
- 37 Katayama, K., Sato, Y., Morotome, Y. et al. (2001) Intermittent hypoxia increases ventilation and  $SaO_2$  during hypoxic exercise and hypoxic chemosensitivity. *J. Appl. Physiol.* **90**, 1431–1440
- 38 Nagasaka, T. and Satake, T. (1969) Changes of pulmonary and cardiovascular functions in subjects confined intermittently in a low-pressure chamber for 3 consecutive days. *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **28**, 1312–1315
- 39 Savourey, G., Garcia, N., Besnar, Y., Guinet, A., Hanniquet, A. M. and Bittel, J. (1996) Pre-adaptation, adaptation and de-adaptation to high altitude in humans: cardio-ventilatory and haematological changes. *Eur. J. Appl. Physiol.* **73**, 529–535
- 40 Roskamm, H., Landry, F., Samek, L., Schlager, M., Weidemann, H. and Reindell, H. (1969) Effects of a standardized ergometer training program at three different altitudes. *J. Appl. Physiol.* **27**, 840–847
- 41 Ricart, A., Casas, H., Casas, M. et al. (2000) Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. *Wilderness Environ. Med.* **11**, 84–88
- 42 Burse, R. L. and Forte, V. A. (1988) Acute mountain sickness at 4500 m is not altered by repeated eight hour exposures to 3200–3550 m normobaric hypoxic equivalent. *Aviat. Space Environ. Med.* **59**, 942–949
- 43 Masuda, K., Okazaki, K., Kuno, S., Asano, K., Shimojo, H. and Katsuta, S. (2001) Endurance training under 2500-m hypoxia does not increase myoglobin content in human skeletal muscle. *Eur. J. Appl. Physiol.* **85**, 486–490

Received 30 April 2003/26 August 2003; accepted 16 October 2003

Published as Immediate Publication 16 October 2003, DOI 10.1042/CS20030161